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(54) N-methyl 11-aza-10-deoxo-10-dihydroerythromycin A, intermediates therefor and processes for their preparation.

(57) Antibacterial N-methyl 11-aza-10-deoxo-10-dihydroerythromycin A and pharmaceutically acceptable acid addition salts thereof, intermediates therefor, and processes for their preparation.

EP 0 101 186 A1

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(54) N-methyl 11-aza-10-deoxo-10-dihydroerythromycin A, intermediates therefor and processes for their preparation.

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(56) References cited:
GB-A-2 047 247
GB-A-2 094 293

Macrolide Antibiotics Chemistry, Biology and Practice S. OMURA, Academic press, p. 87

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Courier Press, Leamington Spa, England.

Description

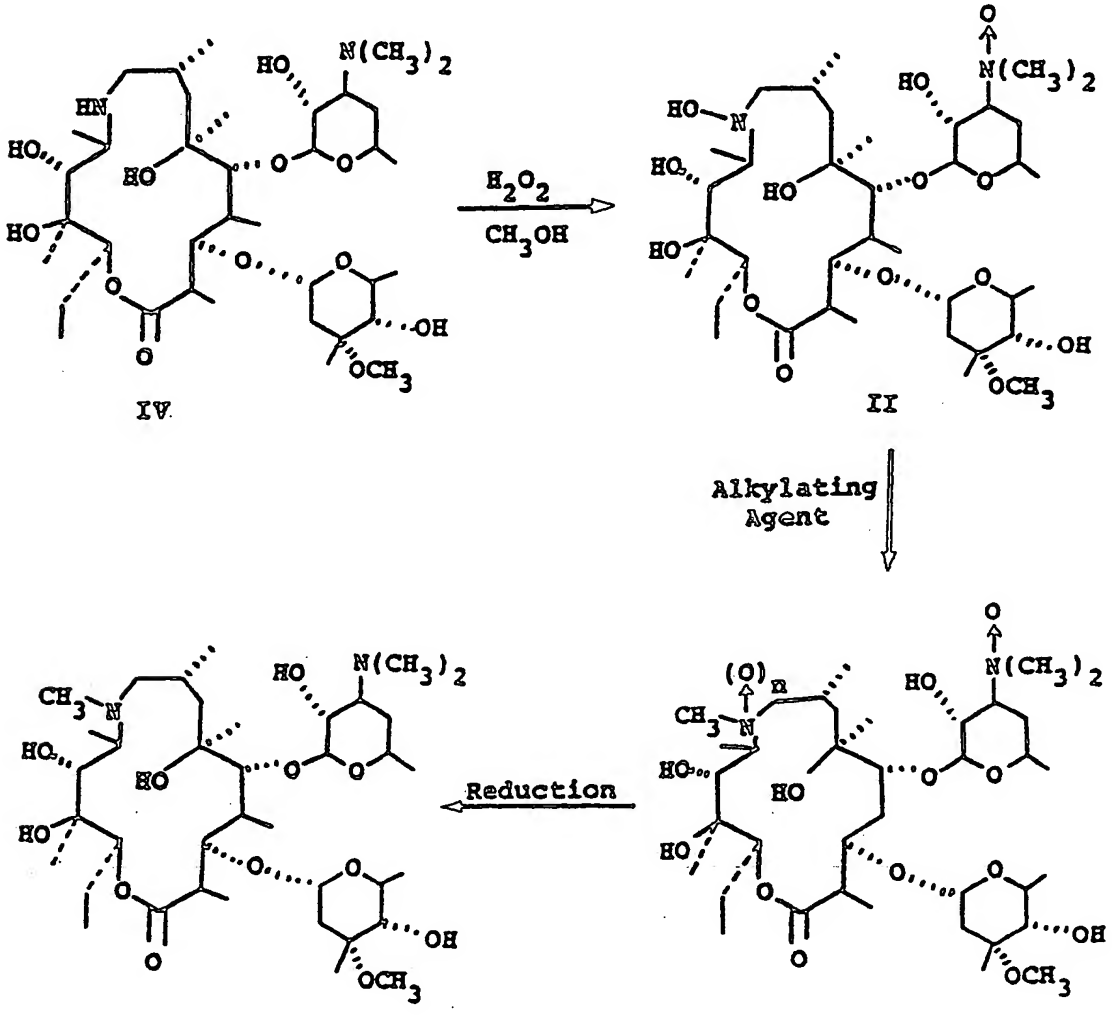
This invention relates to the N-methyl derivative of 11-aza-10-deoxo-10-dihydroerythromycin A, and in particular to a process for its preparation and to intermediates therefor.

Erythromycin A is a macrolide antibiotic produced by fermentation and described in US—A—2 653 899.

N-Methyl-11-aza-10-deoxo-10-dihydroerythromycin A and its derivatives is described in Be—A—892357.

According to the present invention the N-methyl derivative of 11-aza-10-deoxo-dihydroerythromycin A (formula I) is prepared from 11-aza-10-deoxo-10-dihydroerythromycin A (formula IV) by the following reaction sequence:

Reaction Scheme



IV II I III n = 1 III-A n = 0

The compound of formula I can be named as N - methyl - 11 - aza - 4 - O - (L - cladinosyl) - 6 - O - (D - desosaminyl) - 15 - ethyl - 7,13,14 - trihydroxy - 3,5,7,9,12,14 - hexamethyloxacyclopentadecane - 2 - one. However, for simplicity, it is referred to herein as a N-methyl derivative of 11-aza-10-deoxo-10-dihydroerythromycin A, the nomenclature used in U.S. Patent, 4,328,334.

The compound of formula II is named in like manner as N-hydroxy-11-aza-10-deoxo-10-dihydroerythromycin A N'-oxide, the term "N'-oxide" referring to oxide formation on the dimethylamino group of the desosaminyl moiety. The alkylated structure of formula III is named as N-methyl-11-aza-10-deoxo-10-dihydroerythromycin bis N-oxide. The stereochemistry at the 11-aza atom of formula III is not yet known. However, said formula III is intended to embrace the diastereomers.

As an alternative to the nomenclature used above, the parent compound of formula IV below can be named as 9-deoxo-9a-aza-9a-homoerythromycin A. Using this system the compound of formula I is named 9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A.

The oxidation of 11-aza-10-deoxo-10-dihydroerythromycin A is conducted in a reaction-inert solvent, i.e., one which does not react with reactants or products to produce undesired substances, under the conditions of the reaction, using as oxidizing agent hydrogen peroxide. A water miscible solvent should be used.

The oxidation is carried out at ambient temperature; i.e., from about 18°—25°C, for reaction periods of up to 24 hours. An excess of oxidizing agent is used to ensure maximum conversion of 11-aza-10-deoxo-10-dihydroerythromycin A, the limiting reactant. In general, from about 1.0 mole to about 35 moles of oxidant per mole of said limiting reactant is used. In practice, for the sake of economy, from about 5 to about 15 moles of oxidant are used per mole of the limiting reactant. The amine oxide of formula II is isolated by extraction following removal or destruction of the excess oxidizing agent.

The amine oxide of formula II thus produced is then alkylated by reaction with methyl iodide in a reaction-inert solvent and in the presence of an acid acceptor. Representative of reaction-inert solvents useful in this step are methylene chloride, chloroform, tetrahydrofuran and toluene. Suitable acid acceptors are inorganic bases such as alkali metal hydroxides and carbonates, and organic amines such as hindered amine bases, e.g. 2,6-lutidine, said substances being used in at least stoichiometric amount based on the alkylating agent used.

The alkylating agent is generally used in an amount based upon the amine oxide reactant ranging from equimolar to up to 100% excess.

The alkylation reaction, when methyl iodide is used as alkylating agent, is conveniently carried out at ambient temperature.

The intermediate products formed by alkylation of the formula II compound are isolated, if desired, by standard procedures such as evaporation of the reaction mixture following water wash thereof to remove inorganic salts. The reduction products (formula I) of said intermediates are also isolated by standard procedures such as extraction.

It has been found that alkylation of the crude product resulting from the oxidation of IV, gives rise to two products; the compound of formula III identified herein as N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A bis-N-oxide III; and the mono oxide (III—A) wherein oxide formation is at the desosaminyl nitrogen. Said compound is referred to herein as N - methyl - 11 - aza - 10 - deoxo - 10 - dihydroerythromycin A desosaminyl - N - oxide.

The above-described intermediates need not be purified prior to their use in subsequent steps of the above reaction sequence. They can be used in crude form, i.e., as is, following their separation from their respective reaction mixtures. From the standpoint of convenience and economy the intermediates are generally not purified prior to their use in the process of this invention.

The third and final step of the reaction sequence, the reduction step, is carried out either catalytically or chemically on the crude product of the alkylation reaction, or on the individual pure alkylated mono- and bis-oxides (IIIA and III). Catalytic reduction is carried out at ambient temperature (e.g. 18°—25°C) at hydrogen pressures of from about 1 to about 70 bars (atmospheres) in a reaction-inert solvent. Higher temperatures and pressures can be used, if desired, but offer no advantages.

Suitable catalysts are the noble metal catalysts, preferably supported, and certain salts thereof such as the oxides. Representative catalysts are Pd/C, Rh/C, PtO_2 and Raney nickel. The ratio of catalyst to substrate is not critical, but is generally in the range of from 1:1 to 1:2.

Typical solvents for the reduction step are C_{1-4} alcohols, especially ethanol, ethyl acetate and ethers, e.g. tetrahydrofuran, dioxan.

In addition to the above-mentioned heterogeneous catalytic reduction, homogeneous catalysis using, for example, tris(triphenylphosphine)chlororhodium (I), known as the Wilkinson catalyst, can be used. Suitable solvents for said reaction are those enumerated above in connection with the heterogeneous catalyst procedure and in which the homogeneous catalyst is soluble. The concentration of homogeneous catalyst is not critical but, for reasons of economy, is generally kept at levels of from 0.01 mole percent to 10 mole percent by weight based on the substrate.

The hydrogen pressure is not critical but, for the sake of convenience, is generally within the range of from 1.01 to 71,35 bars (1 to 70 atmospheres).

In the above discussions of heterogeneous and homogeneous catalysis, even though the amounts of catalyst which would be used are not generally considered "catalytic" in the normal usage of this term, they are considered as catalytic here since little or no reaction would occur in their absence.

The temperature of the catalytic reductions, heterogeneous or homogeneous, is not critical, but can vary from 20°C to 100°C. The favored temperature range is from 20° to 80°C.

Chemical reduction of the alkylated amine oxides (III—A and III) is accomplished by means of metal hydrides such as sodium borohydride, sodium cyanoborohydride, pyridine-SO_3/potassium iodide, or zinc/glacial acetic acid.

In the Examples presented herein, no effort was made to recover the maximum amount of product produced or to optimize the yield of a given product. The Examples are merely illustrative of the process and of the products obtainable thereby.

Example 1

N-Hydroxy-11-aza-10-deoxo-10-dihydroerythromycin A N'-oxide (Formula II)

To a solution of 11-aza-10-deoxo-10-dihydroerythromycin A (10.0 g) in 40 ml of methanol, a total of 50 ml of 30% aqueous hydrogen peroxide was added dropwise while stirring over a 5—10 minute period. After stirring overnight at ambient temperature, the reaction mixture was poured onto a stirred slurry of ice (200 g), ethyl acetate (200 ml), and water (100 ml). Excess hydrogen peroxide was quenched by cautious dropwise addition of saturated aqueous sodium sulfite until a negative starch-iodine test was indicated. The layers were separated; and the aqueous layer was washed twice with 200 ml portions of ethyl acetate. The three organic extracts were combined, dried over anhydrous sodium sulfate, and evaporated to afford crude N - hydroxy - 11 - aza - 10 - deoxo - 10 - dihydroerythromycin A N'-oxide as a colorless foam (8.6 g).

While the crude product proved satisfactory for use in the preparative procedure described below, purification was readily achieved by silica gel chromatography, eluting with a methylene chloride: methanol:concentrated ammonium hydroxide system (12:1:0.1). Progress of the column was followed by thin layer chromatography on silica gel plates using the system methylene chloride:methanol:concentrated ammonium hydroxide (9:1:0.1). The plates were developed with a vanillin spray [ethanol (50 ml): 85% H_3PO_4 (50 ml): 85% H_3PO_4 (50 ml):vanillin (1.0 g)] indicator with heat. ^{1}Hnmr ($CDCl_3$) delta 3.21 [6H, s,

$$(CH_3)_2N\rightarrow O],$$

3.39 (3H, s, cladinose CH_3O—). MS: major peaks at m/e 576 (ion from desosamine fragmentation), 418 (aglycone ion-minus both sugars). Both peaks are diagnostic for

$$-\underset{|}{N}-OH$$

moiety with aglycone.

In like manner, but substituting hydrogen peroxide by an equivalent amount of peracetic acid, the same compound is produced.

Example 2

N-methyl-11-aza-10-deoxo-10-dihydroeythromycin A bis-N-oxide (Formula III)

To a stirred mixture of N-hydroxy-11-aza-10-deoxo-10-dihydroerythromycin A N'-oxide (4.83 g), methylene chloride (100 ml) and solid anhydrous potassium carbonate (69.7 g), was added 15.7 ml (35.8 g) of iodomethane dropwise under nitrogen over two minutes. The mixture was stirred under nitrogen at ambient temperature for 3.5 hours and the solid which formed recovered by filtration. The filter cake was washed with methylene chloride (250 ml), the filtrate and wash solutions were combined, water (300 ml) was added, and the pH of the vigorously stirred mixture adjusted to 11. The organic phase was separated, dried with anhydrous sodium sulfate, and concentrated to afford crude product as a colorless foam (4.36 g).

While the crude product proved satisfactory for use in the reduction procedure described below, purification was readily achieved by the technique commonly known as "Flash" silica gel chromatography [W. Clark Still, et. al., *J. Org. Chem. 43,* 2923 (1978)] utilizing 230—400 mesh silica gel (silica gel/crude material about 45/1 by weight), eluting by the "flash technique" with acetone/methanol = 4/1 by volume. The 10 ml collected fractions shown to be pure bis-N-oxide by thin layer chromatography (TLC eluting system:methylene chloride:methanol:concentrated ammonium hydroxide = 6:1:0.1; vanillin:85% H_3PO_4:ethanol spray indicator used with heat on silica gel plates) were combined. From 1 gram of crude product, 128 mg of pure bis-oxide was obtained. ^{1}Hnmr ($CDCl_3$) delta 3.20 [9H, broad s, aglycone

$$CH_3-\underset{|}{\overset{|}{N}}\rightarrow O \text{ and } (CH_3)_2-\underset{|}{N}\rightarrow O],$$

3.39 (3H, s, cladinose CH_3O—); MS: m/e 461, and 431,415 (these two peaks are diagnostic for aglycone N-oxide), 159 (cladinose derived fragment), 115 (desosamine N-oxide derived fragment).

The above-described chromatographic procedure also afforded a second, less polar product from the crude N - methyl - 11 - aza - 10 - deoxo - 10 - dihydroerythromycin A desosaminyl - N - oxide (246 mg).

^{1}Hnmr ($CDCl_3$) delta 2.30 (3H, s, aglycone

$$CH_3-\underset{|}{N}-), \quad 3.18 \text{ [6H, s, } \quad -\underset{|}{N}\rightarrow O],$$

3.37 (3H, s, cladinose CH_3O—); MS: major peaks at m/e 461, 156, 115.

Example 3

N-Methyl-11-aza-10-deoxo-10-dihydroerythromycin A

A solution of the crude product of Example 2, comprising N - methyl - 11 - aza - 10 - deoxo - 10 - dihydroerythromycin A desosaminyl - N - oxide and N - methyl - 11 - aza - 10 - deoxo - 10 - dihydroerythromycin A bis-N-oxide (4.36 g), in 150 ml of absolute ethanol was hydrogenated on a Parr apparatus (3.45 bar; 8.0 g 10% palladium on carbon catalyst; ambient temperature) for 1 1/4 hours. The catalyst was filtered, and the resulting filtrate was evaporated to dryness, affording a colorless foam (4.3 g). The crude product was taken up in methylene chloride (100 mml) and then stirred with water (100 ml) while the pH of the mixture was adjusted to 8.8. The organic and aqueous layers were separated. The aqueous layer was then extracted twice with 50 ml portions of methylene chloride. The three organic extracts were combined, dried over anhydrous sodium sulfate and evaporated to afford a colorless foam (3.0 g). The entire sample was dissolved in 11 ml of warm ethanol, and water was added until the solution became slightly turbid. Upon standing overnight. 1.6 g of the title product crystallized from solution; m.p. 136°C, dec. A recrystallization by the same procedure raised the melting point to 142°C, dec ^{1}Hnmr ($CDCl_3$) delta 2.31 [6H, s, $(CH_3)_2N$—], 2.34 (3H, s, aglycone

$$CH_3—\underset{|}{N}—);$$

^{13}Cnmr [$CDCl_3$, $(CH_3)_4Si$ internal standard] ppm 178.3 (lactone, C = O), 102.9 and 94.8 (C—3, C—5), 41.6 (aglycone

$$CH_3—\underset{|}{N}—),$$

40.3 [$(CH_3)_2$—N—]; MS: m/e 590, 432, 158.

Example 4

N-Methyl-11-aza-10-deoxo-10-dihydroerythromycin A

The pure N-methyl-11-aza-10-deoxo-10-dihydroethromycin A bis-N-oxide of Example 2 (20 mg) was hydrogenated according to the procedure of Example 3. Thin layer chromatography with the system methylene chloride:methanol:concentrated ammonium hydroxide (9:1:0.1) and the use of a vanillin spray as indicator (see Example 2) with heat on silica gel plates showed a single, uniform product. Its ^{1}Hnmr and TLC Rf values were identical to those of the product of Example 3. Yield: 60%.

Example 5

N-Methyl-11-aza-10-deoxo-10-dihydroerythromycin A

A solution of crude product of Example 2 comprising N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A desosaminyl-N-oxide and N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A bis-N-oxide (10.0 g) in 150 ml of absolute ethanol was hydrogenated on a Parr apparatus [3.45 bar; 15 g of Raney-Nickel catalyst (water-wet sludge); ambient temperature] for 1 1/2 hours. Work-up as described in Example 3 afforded 8.5 g of the title product, with TLC R_f values identical to those of Example 3.

Example 6

N-Methyl-11-aza-10-deoxo-10-dihydroerythromycin A

A solution of N - methyl - 11 - aza - 10 - deoxo - 10 - dihydroerythromycin A desosaminyl-N-oxide (15 mg) in ethanol (5 ml) was hydrogenated at 1.14 bar (2 psig) using 5 mg 5% Pd-C catalyst for 3 hours. Filtration of the catalyst and solvent removal *in vacuo* produced the title compound (98% yield) as a colorless foam. Its ^{1}Hnmr and TLC R_f values were identical to those of the product of Example 3.

Example 7

N-Methyl-11-aza-10-deoxo-10-dihydroerythromycin A Hydrochloride

To a solution of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (0.2 g, 0.27 mmole) in 50 ml of ethanol (absolute) is added an equimolar amount of hydrogen chloride and the reaction mixture stirred at room temperature for one hour. Removal of the solvent by evaporation under reduced pressure affords the mono-hydrochloride salt.

In like manner, the hydrobromide, acetate, sulfate, butyrate, citrate, glycolate, stearate, pamoate, p-toluenesulfonate, benzoate and aspartate salts of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A, are prepared.

Repetition of this procedure but using twice the amount of acid affords the di-acid salts of said N-methyl derivative.

Example 8

N-Methyl-11-aza-10-deoxo-10-dihydroerythromycin A bis-Hydrochloride

To a solution of 2.00 g of N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A in 50 ml of methylene

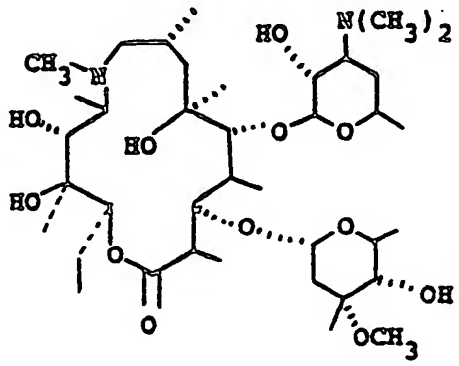
chloride, a solution of 308 mg of pyridinium hydrochloride in 25 ml of methylene chloride was added dropwise over several minutes. The mixture was concentrated to a brittle foam (2.35 g), was thoroughly pulverized in the presence of 125 ml of water. The clear aqueous solution was decanted from the water-insoluble residue and lyophilized to afford the bis-hydrochloride salt of N - methyl - 11 - aza - 10 - deoxo - 10 dihydroerythromycin A as a colorless amorphous foam (1.21 g).

Analysis: Calc'd. for $C_{38}H_{72}O_{12}N_2.2HCl$:
8.65% Cl
Found: 8.69% Cl.

Treatment of a small portion of the water-soluble product with aqueous sodium bicarbonate afforded a water-insoluble product having identical TLC Rf characteristics to those described above for N - methyl - 11 - aza - 10 - deoxo - 10 - dihydroerythromycin A free base.

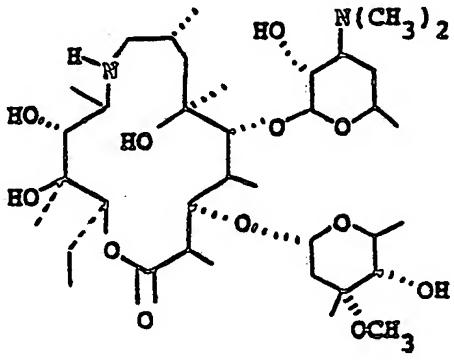
Claims

1. A process for making a compound having the formula



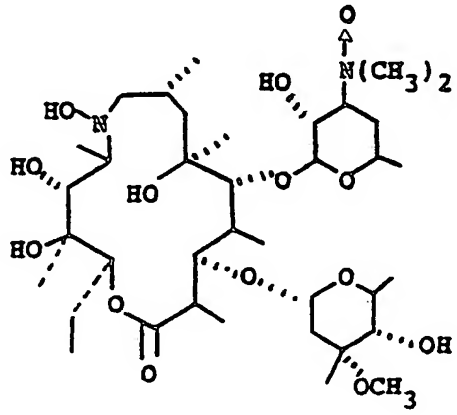
(I)

which comprises the steps of:
(a) oxidizing a compound having the formula



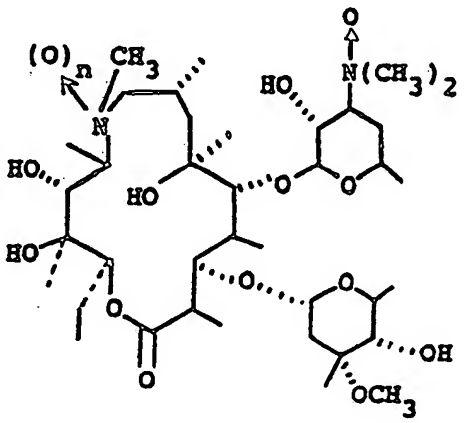
(IV)

with hydrogen peroxide in a reaction-inert solvent to give a compound of the formula:



(II)

(b) alkylating the product of formula II with methyl iodide in a reaction-inert solvent in the presence of an acid acceptor to give a compound of the formula:



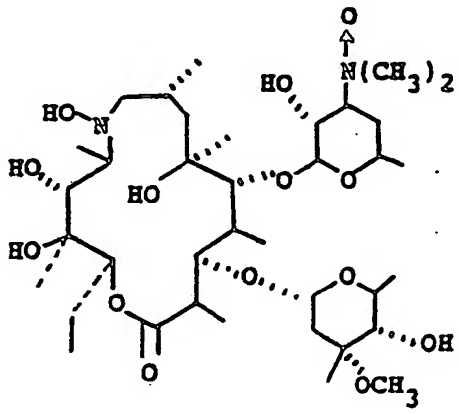
(III)

wherein n is 0 or 1 and

(c) reducing the product of formula III in a reaction-inert solvent with hydrogen in the presence of a noble metal catalyst.

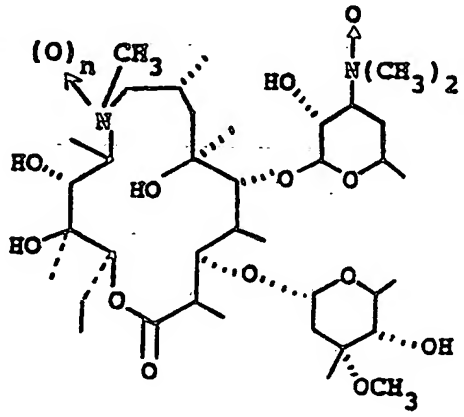
2. The process of claim 1 wherein the noble metal catalyst of step (c) is palladium-on-carbon or Raney-nickel.

3. A compound having the formula



(II)

4. A compound having the formula

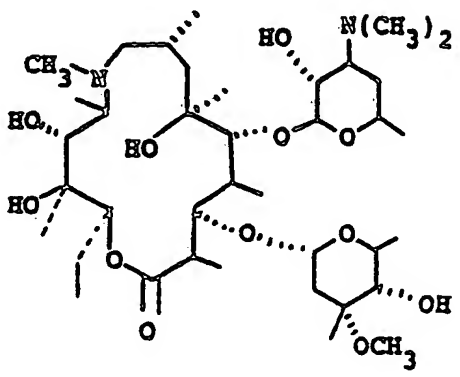


(III)

wherein n is 0 or 1.

Patentansprüche

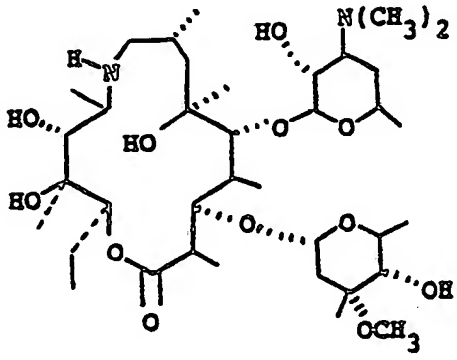
1. Verfahren zum Herstellen einer Verbindung mit der Formel



(I)

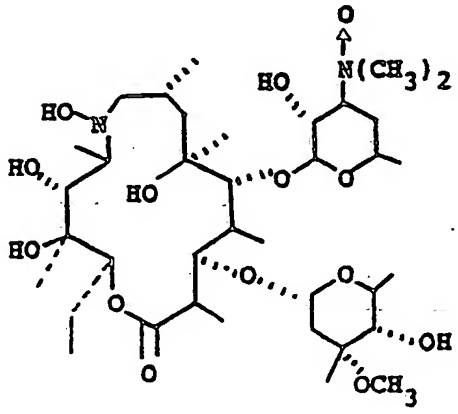
welches die Schritte:

(a) Oxidieren einer Verbindung mit der Formel



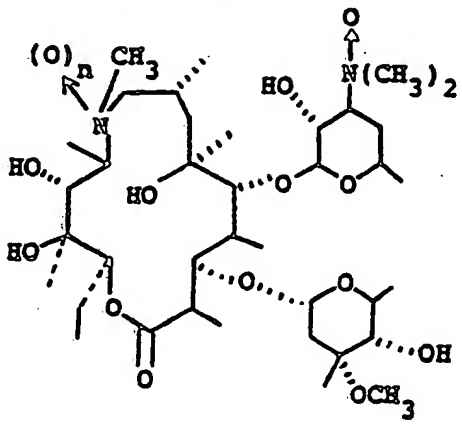
(IV)

mit Wasserstoffperoxid in einem reaktionsinerten Solvent zu einer Verbindung mit der Formel



(II)

(b) Alkylieren des Produkts mit der Formel II mit Methyliodid in einem reaktionsinerten Solvens in Gegenwart eines Säureakzeptors zu einer Verbindung mit der Formel:



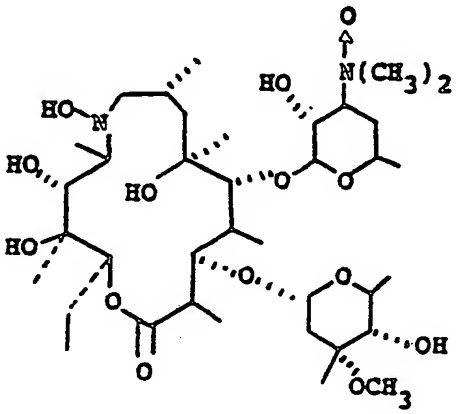
(III)

worin n gleich 0 oder 1 ist, und

(c) Reduzieren des Produktes mit der Formel (III) in einem reaktionsinerten Solvens mit Wasserstoff in Gegenwart eines Edelmetallkatalysators umfaßt.

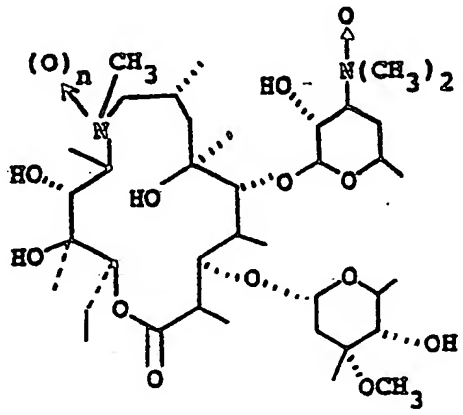
2. Verfahren nach Anspruch 1, worin der Edelmetallkatalysator aus Schritt (c) Palladium auf Kohlenstoff oder Raney-Nickel ist.

3. Verbindung mit der Formel



(II)

4. Verbindung mit der Formel

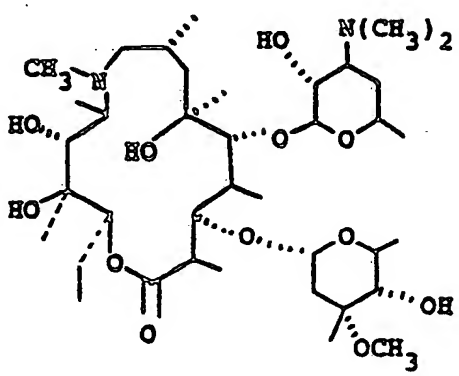


(III)

worin n gleich 0 oder 1 ist.

Revendications

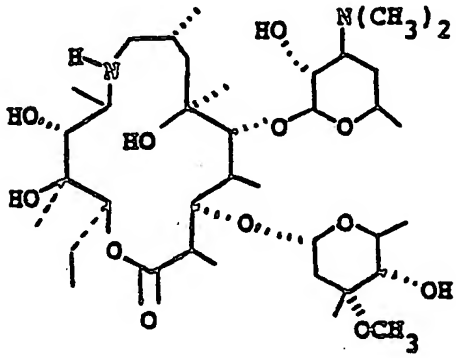
1. Procédé de fabrication d'un composé de formule



(I)

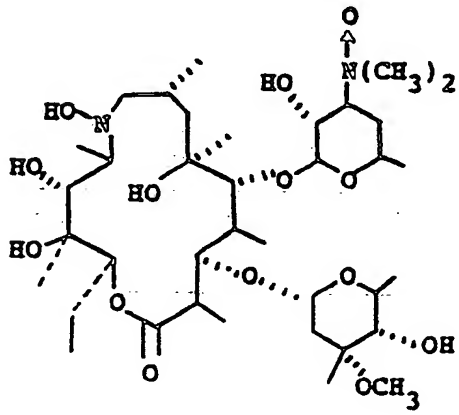
qui consiste à:

(a) oxyder un composé de formule



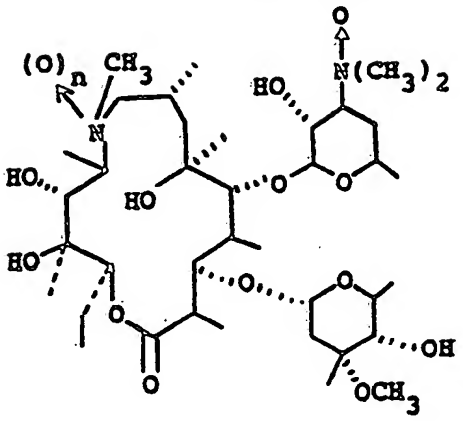
(IV)

avec le peroxyde d'hydrogène dans un solvant inerte vis-à-vis du milieu réactionnel pour donner un composé de formule



(II)

(b) à alkyler le produit de formule II avec de l'iodure de méthyle dans un solvant inerte vis-à-vis du milieu réactionnel en présence d'un accepteur d'acide pour donner un composé de formule



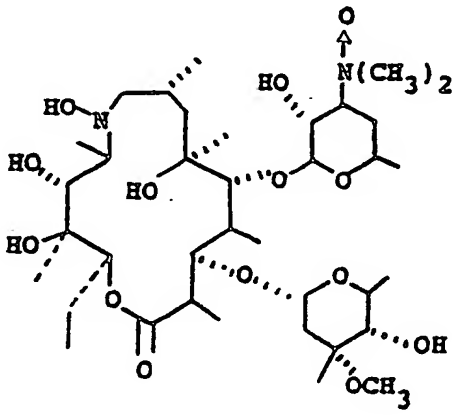
(III)

dans laquelle n est 0 ou 1, et

(c) à réduire le produit de formule III dans un solvant inerte vis-à-vis du milieu réactionnel avec de l'hydrogène en présence d'un catalyseur formé d'un métal noble.

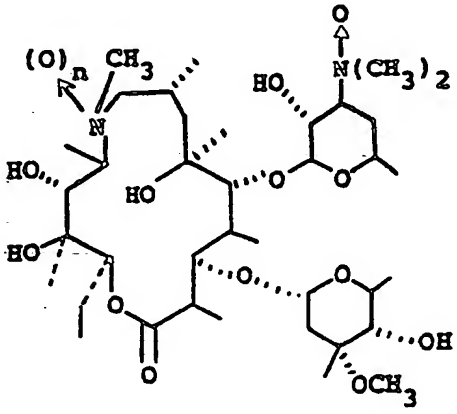
2. Procédé selon la revendication 1, caractérisé en ce que le catalyseur formé d'un métal noble de l'étape (c) est du palladium sur carbone ou du nickel Raney.

3. Composé de formule



(II)

4. Composé de formule



(III)

dans laquelle n est 0 ou 1.